REMARKS

Enclosed is a Notice of Appeal with the necessary fee. Applicant appeals from the Final Rejection mailed on May 5, 2004 rejecting claims 1-5, 8, 9, 11-15, 17-32, 44-55, 57-62, 64, 65, 67-78.

Also enclosed is USPTO form SB96, a Statement Under 37 CFR 3.73(b), and an Associate Power of Attorney from Assignee.

Status of Claims

Claims 1-5, 8, 9, 11-15, 17-32, 44-55, 57-62, 64, 65, 67-78 are pending in the application. Claim 49 is being amended to correct a typographical error.

Double Patenting Rejection

The Examiner maintained the rejection of claims 1-3, 8-9, 11-15, 17-22, 27-32, 44-55, 59-62, 64-65, 67-71 and 72-78 under the judicially created doctrine of obviousness-type double patenting as being unpatentable over claims 1-5, 7-23, 25, 27-30, 34-37, 41-45 of copending Application No. 09/568,818.

As acknowledged by the Examiner, when either the present case or the 09/568,818 case is indicated as allowable, the double patenting issue will be addressed in the other case.

Rejection Under 35 U.S.C. § 112 of Claims 72-74 and 77-78

The Examiner rejected claims 72-74 and 77-78 under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement on grounds that the original disclosure does not provide support for the saturated phospholipid's being zwitterionic.

The 112 rejection is respectfully traversed because on page 8, lines 22-26,

the Specification recites:

> In contrast, addition of calcium ions leads to a dramatic improvement in the stability of the dry phospholipid-based powder to humidity. While not being bound to any theory, it is believed that calcium ions are believed to intercalate the phospholipid membrane, thereby interacting directly with the negatively charged portion of the zwitterionic head group.

Thus, the Specification provides support for claims 72-74 and 77-78 by reciting that the saturated phospholipid can be a zwitterionic phospholipid.

Rejection Under 35 U.S.C. § 103(a) of Claims 1-5, 8-9, 11-15, 17-32, 44-55, 57-62, 64-65 and 67-78

The Examiner rejected claims 1-5, 8-9, 11-15, 17-32, 44-55, 57-62, 64-65 and 67-78 under 35 U.S.C. 103(a), as being unpatentable over Weers et al. (6,309,623) in view of Materne et al. (GB 2065659). The rejection is respectfully traversed.

Weers at al. does not teach a particulate composition for delivery to the pulmonary system, the composition comprising particles comprising an active agent, *a saturated phospholipid and a polyvalent cation, wherein the molar ratio of polyvalent cation to phospholipid is at least 0.05 and is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation*, as recited in Claim 1.

Weers at al. teaches that "in particularly preferred embodiments, the structural matrix is associated with, or comprises, a surfactant such as, a phospholipid or fluorinated surfactant." Weers et al. explains that "although not required, the incorporation of a compatible surfactant can improve the stability of the respirator dispersions, increase pulmonary deposition, and facilitate the preparation of the suspension." Thus, Weers at al. teaches the use of phospholipids as surfactant additions to improve the stability of respiratory dispersions of particles. (Column 15, line 62 to about 16 line 2.) Weers at al. further teaches that the lipid surfactants should have particular gel to liquid crystal phase transition temperatures:

"Lipids, including phospholipids, from both natural and synthetic sources are

> particularly compatible with the present invention and may be used in varying concentrations to form the structural matrix. Generally, compatible lipids comprise those that have a gel to liquid crystal phase transition greater than about 40° C."

(Column 16, lines 44-49). Thus, Weers et al. teaches the use of surfactant lipids, such as phospholipids to improve the stability of respiratory dispersions of particles, and also teaches that the lipid surfactants should that have a gel to liquid crystal phase transition temperature of greater than about 40°C.

While Weers et al. teaches the desirability of selecting a "compatible" phospholipid surfactant having a particular gel to liquid crystal phase transition temperature; Weers et al. does not teach particles comprising phospholipid which has been chemically modified by a divalent cation in a particular minimum molar ratio, to have a gel to liquid crystal phase transition temperature that is higher than that of the unmodified phospholipid, as claimed. Specifically, Weers et al. teaches that the problem of compatibility of the lipid addition to the other particle constituents is easily solved by selecting phospholipids which have particular minimum gel to liquid crystal phase transition temperatures. Thus, Weers at al. teaches against the more complex and difficult to achieve solution of modifying the structure of a phospholipid with a divalent cation in the claimed molar ratio to obtain a higher gel to liquid transition temperature. Clearly, one of ordinary skill in the art would not have the motivation to devise this more complex chemical solution to increase a gel to liquid transition temperature of a particular phospholipid, when it is taught by Weers et al. that the compatibility problem can be easily solved simply by selection of an appropriate phospholipid from those that are readily commercially available.

The Examiner acknowledges that Weers et al. lacks an exemplification of a composition comprising saturated phospholipid and divalent cation, and a teaching of the ratio of cation to phospholipid. But it is more than that, because Weers et al. simply does not teach or suggest a particle comprising phospholipid which has been chemically altered to provide an increased gel to liquid crystal phase transition temperature with the particularly claimed molar ratio of polyvalent cation of greater than 0.5.

The Examiner continues to suggest that Materne et al. teaches calcium phosphatidycholine for pharmaceutical preparations, and also teaches a molar ratio of cation to phospholipid of 0.5:1 to 2:1. The Examiner further states that such a ratio is taught as highly stable for pharmaceutical formulation.

However, Materne et al. teaches the addition of calcium chloride to an unsaturated phospholipid, and not a saturated phospholipid as claimed in claim 1. As explained in the previously submitted Declaration of Dr. Weers under Rule 1.132 submitted on November 25th, 2002, Materne et al. does not teach a saturated phospholipid, but instead only describes the use of calcium chloride in combination with unsaturated phosphatidylcholine. (Para 5, Weers Declaration.) Materne et al. teaches phosphatidylcholines that are plastic materials of low stability, and difficult to process and handle. This description of physiochemical properties and appearance corresponds to phosphatidylcholines that are unsaturated, whose particle diffuse into large conglomerates due to temperature or moisture induced aggregation. (Para 5, Weers Declaration) In contrast, saturated phosphatidylcholines arrive from vendors as flowable powders which are typically chemically stable because they contain no double bonds that can be oxidized; thus, these materials are not difficult to handle under ambient conditions. Materne et al. further describes the phosphatidylcholines as being yellow in color - which is also indicative of oxidation processes involving double bonds present in unsaturated materials. In contrast, saturated phosphatidylcholines are generally white in appearance. (Para 6, Weers Declaration.) Thus, Materne et al. clearly teaches the use of unsaturated phospholipids and not saturated phospholipids.

The instant claims are to particles comprising saturated phospholipids in combination with a polyvalent cation in a molar ration that increases the Tgel-liq transition temperature of the particles. As demonstrated by Dr. Weers in Fig. 1 and Para 9 of the declaration, the addition of calcium chloride to unsaturated phospholipids of the type described by Materne et al. does not significantly increase the Tgel-liq; whereas, unexpectedly, the addition of calcium chloride to a saturated phospholipid as claimed, provides a significant and large increase in gel to liquid crystal transition temperature. The

inventive aspect of a particle comprising a saturated phospholipid in combination with a polyvalent cation in a particular molar ratio to provide a higher gel to liquid transition temperature is an unexpected result that warrants grant of patent rights to Applicant.

Furthermore, Materne et al. does not provide any motivation for substituting a saturated phospholipid for the described yellow, low stability, unsaturated phospholipid. Materne et al. teaches a particular molar ratio of calcium chloride to unsaturated phospholipid, but not a particular molar ratio of polyvalent cation to saturated phospholipid which in chemical combination provides a higher gel to liquid transition temperature. Thus, Materne et al. does not cure the deficiencies of Weers et al. Instead, the Examiner appears to be reconstructing the teachings of Claim 1, in hindsight, and without any motivation in the cited references to perform the particularly claimed combination.

The Examiner further states that it would have been obvious to exemplify a suspension medium comprising calcium chloride and dipalmitoylphosphatidylcholine because Weers et al. exemplifies a composition comprising dipalmitoylphosphatidylcholine and teaches adding salts that fine tune the stabilized dispersions for maximum life and ease of administration. The Examiner then states that discovery of the optimal or workable ranges as claimed involves only routine skill in the art.

However, it is not clear that Weers et al. teaches the addition of a divalent salt to fine tune a stabilized dispersion for maximum life and stability. Instead, as acknowledged by the Examiner, Weers et al. teaches that "[I]norganic salts such as calcium chloride are taught as optional excipients, which adjust pH." [Emphasis added. With regard to the addition of divalent salts, Weers et al. actually states at the end of the paragraph describing excipients that: "[t]he inclusion of both inorganic (e.g. sodium chloride, calcium chloride), organic salts.... and buffers is also contemplated." But Weers et al. does not mention why such a combination is desirable and does not teach the molar ratios used in the present claim. Thus, at best, Weers et al. teaches addition of various compounds to stabilize a dispersed solution, not to increase the gel to liquid transition temperature of a phospholipid within a particle.

Weers et al. teaches addition of calcium chloride as an optional inorganic salt addition, without providing a reason for the addition of the calcium salt. Weers et al. also does not teach or recognize a particle comprising a composition of phospholipid and divalent salt in a molar ratio that increases the gel to liquid transition temperature of a phospholipid. Nor does Weers et al. make any mention of a specific molar ratio of polyvalent cation to phospholipid that is at least 0.05, or that the molar ratio is sufficiently high to increase the gel-to-liquid crystal transition temperature of the particles compared to particles without the polyvalent cation, as recited in Claim 1. There is simply no motivation suggested or taught by Weers et al. to derive the particles of claim 1.

Furthermore Applicant respectfully disagrees with the Examiner's admonishment that the claim is wholly functional and recites functional language at the point of novelty. Claim 1 clearly recites a particulate composition (which has structure) comprising particles (also structure) a combination of chemical compounds, including active agent, and saturated phospholipid and divalent cation in a minimum molar ratio of at least about 0.5 (list of compounds with specific numeral molar ratio limitation). Even the functional definition is defined in terms of achieving a gel to liquid temperature that is higher than the gel-to-liquid crystal transition temperature of the particles without the polyvalent cation. Thus, the claim defines much more than just a functional definition at the point of novelty.

Thus, the cited combination of Weers et al. and Materne et al. simply does not sustain a prima facie obviousness rejection of claim 1, which recites a saturated phospholipid, a polyvalent cation, and a molar ratio of the two compounds that is higher than 0.5 to increase the gel to liquid transition temperature of the phospholipid containing particle. For these reasons, claim 1, and claims 2, 5, 8, 9, 11-15, 17-30, 53, 54 and 72, which depend upon claim 1, are not rendered unpatentable by Weers et al. and Materne et al.

Independent claims 31, 32, 44 and 59, all of which recite the molar ratio of polyvalent cation to saturated phospholipid 1 of at least 0.05 are also not rendered unpatentable by Weers et al. and Materne et al. for the same reasons. Claims 45-52, 55,

57, 58, 60-62, 64, 65, 67-71 and 73-78 also depend from one of claims 31, 32, 44 and 59, and are also allowable over Weers et al. and Materne et al.

Independent claims 72-78 are also patentable for the same reasons as claim 1, namely that the cited references do not teach a molar ratio of polyvalent cation to saturated phospholipid 1 of at least 0.05. In addition, Weers et al. and Materne et al. do not teach a particulate composition comprising a saturated, zwitterionic phospholipid as taught in claims 72-74, 77, and 78, nor do the cited references teach hollow particles as claimed in claim 76. For these reasons, claims 72-78 are independently allowable over the cited references.

CONCLUSION

For the foregoing reasons, allowance of the instant application is respectfully requested. Should the Examiner have any questions regarding the above amendments or remarks, the Examiner is requested to telephone Applicant's representative at the number listed below.

Respectfully submitted,

JANAH & ASSOCIATES, P.C.

Date: November 5, 2004 By: _____

Ashok K. Janah
Reg. No. 37,487

Please direct telephone calls to:

Ashok K. Janah
(415) 538-1555

Please continue to send correspondence to:

Guy Tucker
Nektar Therapeutics
150 Industrial Road
San Carlos, CA 94070.